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The Gut-Brain Axis: Treating Depression Through Microbiome Alterations

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Abstract

The purpose of this research and literature review is to explore the possible role that gut microbiome alterations have in the treatment of neurobehavioral diseases; specifically, anxiety and depression. This literature review searched PubMed, CINAHL, and Clinical Key. A variety of key terms were used during the search. Due to the field of research being relatively new and limited, studies from the last ten years and animal models were included in the study. Studies were excluded due to poor design or if the studies did not include anxiety or depression in the research. The research shows that there are the are multiple pathophysiologic pathways leading to the development of anxiety and depression. However, that the gut plays a much larger role in brain health than previously thought. Additionally, this study explores probiotics as a possible treatment for depression and anxiety. The research also shows a correlation between pathologic bacteria, inflammatory pathways, and a reduction in neurotransmitters associated with behavioral health. The limiting factors of this research was sample size, as many of the studies were conducted as pilot studies, as well as variations in the dosage of probiotics used in the control trials comparing probiotics to placebos. Overall, the research shows promise, but larger studies would be needed to establish guidelines recommending microbiome alterations as a treatment of anxiety and depression.

Keywords: fecal transplant, gut microbiome, depression, anxiety, mood disorders, and probiotics.

Introduction

In recent years, there has been extensive research in the microbiome of the gut as a contributing factor to many diseases. Alterations in the natural flora of the gut has been implicated in multiple illnesses and more recently in patients with mental health disorders. The purpose of this study is to critically analyze research regarding the effects of alterations within our natural gut flora and treatment of neurobehavioral disorders through diet and microbiota transplantation in comparison to other currently recommended treatments. It is anticipated that this systematic literature review will show beneficial outcomes to patients using microbiota transplant as treatment of neurobehavioral disorders with an emphasis on depression and anxiety.

Statement of the Problem

Mental illness is among the most prevalent and costly disorders to treat. A recent study released by the Centers for Disease Control (2018) found that 8.1% of Americans reported suffering from symptoms of depression. More than 80% of those affected, reported problems in multiple areas of their lives. Among patients with depression, as many as 85% reported having significant anxiety. Patients with diagnosed anxiety had a similar occurrence of depression. While combination treatment of cognitive behavior therapy and pharmacotherapy have proven beneficial in many patients, there are many individuals that do not respond to treatments, and compliance to therapy may be an issue. It is also estimated that 40% of patients with depression do not seek treatment (CDC, 2018). By identifying changes in the microbiome of patients with anxiety and depression, treatment can be aimed at treating the underlying pathology and not just masking symptoms while the patient is receiving treatment.

Research Questions

In patients with depression or anxiety, do gut microbiota transplants improve symptoms of depression?

In patients with depression or anxiety, is there an alteration in gut microbiota associated with the development of moods disorders?

Methods

A literature review was performed using the following electronic databases: PubMed, CINAHL, and Clinical Key. Both MESH and keywords (*fecal transplant, gut microbiome, depression, anxiety, mood disorders, and probiotics)* were used to define a selection of literature discussing gut microbiome alterations and the use of transplants and modulations as possible treatment of mood disorders with an emphasis on anxiety and depression. Peer-reviewed studies from the previous ten years were included, in addition to animal studies. Studies were excluded due to poor design or not including anxiety or depression in the research.

Literature Review

For many years, it has been known that gut microbiota played major roles in intestinal function. A review of the literature shows that there is emerging evidence gut microbiomes effect on overall health, immune function, and the nervous system. There is now evidence of a bidirectional relationship between the gut microbiota and the brain, which is called the microbiota-gut-brain (MGB) axis. Alterations within the MGB axis have now been established in patients suffering from many disease states, including, but not limited to, mood disorder, autism-spectrum disorder, multiple sclerosis, attention-deficit hypersensitivity disorder, and obesity. The review shows the underlying pathology is related to bacterial imbalances, gut leakage, and generalized inflammation (Petra et al., 2015).

Gut microbiome and the link to depression and anxiety

In order to research gut microbiome alterations as a form of therapy, a bidirectional relationship must first be established.

Berk et al. (2013) evaluated depression and anxiety as an inflammatory disease. As experts in their field of psychiatry, this article was written to establish connections between the gut, inflammation, and the brain. By establishing a pathway, research can be conducted exploring this pathway, which is the goal of Berk. The main question the study attempts to answer is what factors cause this low-grade inflammation, which is shown as a clear link to multiple mental illnesses, including depression and anxiety. In addition to stress, trauma, smoking, obesity, and diet, it identifies a new pathway between the gut and brain; the toll-like receptor (TLR) IV pathway. In patients with clinical depression, they have been shown to have increased levels of immunoglobulin A (IgA) and immunoglobulin M (IgM) directed at the lipopolysaccharides (LPS) of multiple gram-negative bacteria that are present naturally within our gut flora. The LPS, also referred to as endotoxins, are toxic substances and activate proinflammatory cytokines, including: tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), and cycloxegenase-2 (COX-2). This systemic immune response indicates that the normal gut barrier has been broken and has become more permeable. This review discovered that patients with clinical depression had significantly higher levels of IgM directed at LPS when compared to patients without depression.

Mood disorders are believed to have multiple pathologic pathways, however, pathways between the gut and CNS were not hypothesized until recently. This study helps locate specific chemicals within the gut, serum, and CNS that can be implicated in causing the inflammatory changes that are present in mood disorders such as, anxiety and depression. Mood disorders have

long been treated by replacing neurotransmitters with medications. By identifying inflammatory markers that cause the reduction in neurotransmitters, treatments can be modulated to treat the inflammation before it causes the reduction in neurotransmitters.

To further establish a gut-brain pathway as a source of the development of mood disorders, Inserra, A, Rogers, G, Licinio, J, and Wong, M. (2018) evaluated inflammatory markers and bacteria overgrowth in patients with major depressive disorder (MDD) and anxiety. Within the study, they propose a bidirectional relationship between the gut and brain function. They hypothesize that in patients with increased symptoms of depression, there was increased NLRP3 inflammasome triggering and subsequently increased activation of IL-1 and TNF-mediated pathways. This links exposure to psychological stress, immune system function, gut microbiome composition, and psychological stress response to increased systemic inflammation and depressive symptoms. The heightened inflammatory state decreases the bioavailability of neurotransmitters and their precursors.

The goal of this article was to establish a need for further research by establishing the relationship between the gut and brain. In order to prove this, Inserra et al. (2018) also reviewed multiple trials that evaluated the microbiome and bacterial families in patients with depression to help support their hypothesis. They found an increased growth of proinflammatory bacteria and undergrowth of multiple species of bacteria with anti-inflammatory properties. Additionally, they evaluated clinical trials that used psychobiotics to treat symptoms of depression. These clinical trials that were reviewed were minimal in time and had limited participants but showed promising results. This study shows promise for understanding pathophysiology and etiology of mood disorders, but the limitation to this study is that further investigation would be required for definitive treatment recommendations.

Patients with Major Depressive Disorder (MDD) demonstrate metabolic disorders within their gut. A study by Xueyan, J., Cui, W., Changxin, W., and Xuemei, Q., (2019) further investigated the molecular changes and timing of these changes that occur in patients with MDD. In order to accomplish this, they created an animal model using rats and inducing depression-like symptoms through chronic unpredictable mild stress (CUMS). In this randomized control trial, twelve rats were randomly assigned to CUMS or to the control groups and housed in identical environments. Within these environments, the rats had access to plain water or sucrose. The rats were then stressed for four weeks, in random order, every day. Fecal samples, blood samples, and body weights were collected at identical intervals. The metabalomes in the fecal and blood samples were evaluated using temporal dynamic gas chromatography-mass spectrometry (GC-MS) to establish the exact timing of gut microbiome changes and the development of MDD symptoms. Additionally, twelve neurotransmitters within the hippocampus were evaluated and quantified to correlate with fecal and blood samples. The rats were then tested on sugar preference, grooming time, time spent immobile, rearing counts, and body weight.

The results of this study revealed that after 4 weeks there was statistical significance in rats that were exposed to the CUMS protocol versus the control rats. CUMS rats had a significant increase in body weight ($P < 0.05$), time spent immobile ($P < 0.01$), and rearing counts ($P < 0.001$). There was no statistical significance in sucrose preference or grooming time. Analysis of the blood and fecal metabolome in the rats exposed to CUMS protocol also showed a significant remodeling in the rats with depressive-like behaviors ($P < 0.05$). The quantification of all twelve neurotransmitters were all significantly lower in the CUMS rats ($P < 0.05$). These results indicated that chronic stress can not only change our behavior, but changes the physical composition of our gut. This link helps to establish the relationship that our gut and brain have in

regards to neurological health. By measuring the changes in gut microbiome and quantitative changes in neurotransmitters that directly affect neurological function, a bidirectional link is clearly established. The strengths of this study are the identical environments and the fact that the trial was randomized. The weakness of the study is the number of participants. While this study lays a good foundation, further larger studies involving humans would need to be performed.

In order to establish a causative relationship between gut pathologic bacteria and mental health, Kelly et al. (2016) transferred gut microbiome from patients with depressive and anxiety disorders into rats with a depleted gut microbiome. They theorized that by transferring the microbiome of patients with clinical depression they could confirm the role that gut-brain neural pathways contribute to. They accomplished this by using 34 patients with clinical depression and 33 control patients with no disease. They were cross matched for age, gender, and ethnicity. Fecal samples were extracted from all individuals. Rats were pretreated, once daily, with ampicillin, metronidazole, vancomycin, ciprofloxacin, and imipenem for 28 days. The rats were then matched for body weight and sex and colonized with the donors' microbiome 70 hours later. Booster doses on donor microbiome were given twice weekly to reinforce phenotype and prevent error.

Statistical analysis used data that was normally distributed according to Shapiro-Wilk test and using unpaired t tests. Grubb's test removed outliers. There was found to be no significant difference in daily diet ($t(61) = 2.06$, $P = 0.05$). Assessment of proinflammatory markers showed significant increase in interleukin 6 ($t(62) = 2.69$, $P=0.009$), interleukin 8 ($t61) = 2.37$, $P=0.021$), TNF-α ($t(49) = 2.36$, $P = 0.022$), and C-reactive protein ($t(45) = 3.6$, $P = 0.001$) when compared to healthy controls. Gut microbiomes were also found to have statistically altered families of bacteria in the depression sample ($P = 0.03$). Rats that received fecal microbiota transplants

(FMT) from patients with depression demonstrated more behaviors of depression and anxiety. This was assessed with differences in a reduction of total activity in an open field (P=0.013) and decreased visit to open arms in the elevated plus maze (P = 0.029). Overall, the study demonstrated that there is a link between stress, inflammation, gut microbiome, and brain neural health. The limitation of this study is that it was performed in rats and the correlation to human microbiota may differ.

Luo et al. (2018) attempted to prove the link between certain bacteria and the upregulation of inflammatory pathways associated with increased levels of inflammation in patients with depression and anxiety. They hypothesized that the lack of protective bacteria and overgrowth of "depressive bacteria" increased basal cortisol levels and inflammation. In order to prove this theory, they raised germ-free (GF) mice, specific antigen-free mice who were treated with E. Coli LPS, and mice treated with fecal transplants from patients with clinical depression. In order to maintain gut microbiomes consistent with their control and test groups, the rats were kept in identical, sterile environments and fed autoclaved feed.

The results of this study were achieved by comparing the behaviors of GF and depression-FMT mice. There was a significant difference in which the GF mice showed greater antianxiety-like behaviors and higher locomotion by performing better in the open-field test (OFT). They had an increased total distance ($p<0.05$) and increased center distance ($p < 0.001$) when compared to the mice treated with FMT from depressed patients. This portion of the study is important because it establishes a link between gut microbiome contents and behaviors.

While GF mice showed less behaviors linked to anxiety and depression in initial evaluation, they were found to have an upregulation in 23 of 84 glucocorticoid receptor pathways. The altered genes in the GF mice were identified as being highly associated with

neurological disorders. The upregulation of glucocorticoid pathways causes a heightened stress reaction to acute stressors by increasing total amount of corticosterone and stress hormones that are released. This suggests that the lack of pathologic gut microbiome leads to antianxiety and antidepressant behaviors, but total lack of gut bacteria decreases the host's ability to react to acute stressors without increasing inflammation. Increased inflammation correlates with the etiology of many pathologic conditions including, but not limited to, mood disorders, further enforcing the delicate relationship between the brain and gut.

In an attempt to prove the correlation of gut microbiome composition and depression in humans, Naseribafrouei et al. (2014) performed a partially double-blind study. They had assessed the research regarding animal models and wanted to pinpoint specificities in the human model. In order to prove this, they recruited 37 patients from a mental clinic with depression ranging from mild to severe, and 18 control patients with no diagnosable depression. The control group was recruited based on similar age and gender distribution.

Fecal samples were collected from all participants and were analyzed using DNA extraction and sequencing, which has been previously validated during irritable bowel syndrome (IBS) research. The results showed that there were no significant differences in bacteria species richness or diversity between the depressed and control group. However, there was a significant correlation of underrepresentation of Bacteridetes phylum ($p<0.05$). This is consistent with previous studies that associate low Bacteroidetes with obesity and low-grade inflammation. Overgrowth of Alistipes ($p<0.007$) and Oscillibacter ($p<0.03$) were both associated with the depression group. Of note, Oscillibacter has valceric acid as its main metabolite. Valceric acid will bind to gamma-Aminobutyric acid-a (GABAa) receptors because it is structurally similar to GABA. While the role of valceric acid in the gut is unclear, its overgrowth can be associated

with decreased GABA binding and therefore, correlates with the pathophysiology of depression. The weakness of this study is a small sample size, but is beneficial to this study because it shows specific bacteria associated with the development of mood disorders.

A study by Zheng et al. (2016) evaluated the gut microbiome of patients with MDD by analyzing alterations in gut bacteria and hippocampal metabolism. Like similar studies performed by this group, fecal transplants from patients with MDD were transplanted into mice and multiple tests assessing anxiety and depressive-like behaviors were evaluated. This study evaluated 58 MDD patients and 63 healthy controls. In order to further establish a causative role, this study attempts to dive farther and specifically identify bacterial families and metabolic pathways within the hippocampus that are affected. Fecal transplants were randomly chosen from those with MDD and healthy patients to colonize the mice. They were kept in separate environments to prevent cross-contamination. Behavioral tests were performed at one and two weeks. After the second week, the mice were killed, and fecal samples immediately collected.

It was well documented in this study and their previous cohort study that fecal transplants from patients with depression induce depressive-like behaviors in mice. This is exhibited in decreased performance in the center motion distance on OFT and increased immobility ($p<0.05$). Further examination through DNA extraction of gut microbiome in patients with MDD showed an overrepresentation of 29 bacterial families. Of special interest were three species that were implicated as playing a more integral role in depressive symptoms; phylum Firmicutes, Bacteriodetes, and Actinobacteria. In addition, the hippocampi of all mice within the study were compared and found to have profound differences in metabolic pathways involving carbohydrates and amino acids. Other anatomical areas of the brain were not addressed in this study. This does provide some limitation to this study because depression and anxiety are known

to affect multiple regions within the brain. An additional limitation to this study was that it identified gut bacteria alterations in MDD, however, other neuropsychiatric disorders were not evaluated.

Gut microbiome transplants as therapy

Now that the relationship between the gut and brain has been established, treatment involving alterations of the gut microbiome can be further researched. Multiple methods have been studied regarding how to replace pathologic bacteria, but in the interest of this study, direct replacements of microbiome are being evaluated.

Akkasheh et al. (2016) performed this eight-week, randomized, double-blind, placebo-controlled trial to evaluate the effects of probiotics on depressive symptoms in patients with MDD as defined by the Beck Depression Inventory (BDI). Forty patients were included and randomly assigned to intervention and placebo groups. The intervention group included a once daily, probiotic supplementation of Lactobacillis casei and Bifidobacterium bifidum. Dietary and activity logs were collected from the enrolled members and showed no significant difference. The patients were also instructed not to change their daily habits or dietary intake during the trial.

In addition to evaluating the BDI at the end of the studies, other secondary markers such lipid concentrations, fasting blood glucose (FBG), C-reactive protein (CRP), total antioxidant capacity (TAC), and glutathione (GSH) were monitored to evaluate insulin metabolism and oxidative stress. Five patients left the study, leaving a total of 35 patients that participated in the study. A 90% compliance rate was achieved in the daily administration of probiotic or placebo capsules.

The eight-week reevaluation of the BDI scores showed that the participants receiving the probiotic capsules had significantly lower scores ($p<0.001$) when compared to the placebo group. Also, they were found to have statistically significant lower insulin levels ($p<0.03$) and hs-CRP ($p<0.03$) and statistically higher levels of GSH ($p<0.02$). There was no statistical significance in levels of lipid profiles, FPG, or TAC. Limitations of the study were short duration and small sample size. Also, since multiple probiotic strains were administered simultaneously, it is unclear which strain caused the observed effect.

Bambling, Edwards, Hall, and Vietta (2017) performed a small, single group, intervention-only study, which included 16 qualifying participants with depression that was resistant to selective serotonin reuptake inhibitors (SSRIs). This study was a follow-up to a previous study that showed promising results, but only had four participants. The goal of the study was to assess the role that probiotics play in reducing symptoms of depression in combination with standing treatments. This was done by evaluating participants using BDI, Outcome Questionnaire 45 (OQ45) and Quality of Life (QoL). Participants were treated with their current medication regimen along with adding daily dosing of probiotics. The study intervention included twice daily dosing of probiotic capsules with Lactobacillus acidophilus, Bifidobacterium bifidum, Streptococcus thermophiles and magnesium orotate.

Sixteen participants completed the study with good adherence to the intervention. At the eight-week mark, there was statistically significant lower BDI scores ($p = 0.005$) and OQ45 ($p = 0.001$). There were borderline statistically significant changes in QoL scores ($p = 0.052$). Limitations of this study are small sample size, however; this study serves as a pilot study and did indicate a need for a larger study. It does correlate with the previous research that has shown

improved depression scores with the administration of magnesium orotate. It also must be noted that the lack of a control group does weaken the study, but shows the need for further research.

Within the central nervous system (CNS), gamma-Aminobutyric acid (GABA) receptors play a significant role in neuronal function and health. Alterations in GABA receptors are believed to play a vital role in the development of mood disorders, such as depression and anxiety. A study by Bravo et al. (2011) observed that treatment with Lactobacillus rhamnosus (JB-1) modulates the expression of multiple GABA receptors within the CNS. Additionally, they observed that administration of JB-1 reduces corticosterone level associated with a stress response. When monitoring behaviors, mice fed with JB-1 showed more antidepressant behaviors and less activities associated with anxiety. This implies the HPA axis and bidirectional relationship between the gut and brain.

This study establishes a pathological gut-brain connection in patients with mood disorders and is essential to establishing possible treatment through gut modulation. The data suggests that by treating patients with nonpathogenic bacteria, we can target and alter the receptors within the CNS that are causative of neurobehavioral disease. Specifically, the GABA receptors which are currently the target of pharmacological interventions. The weakness of this study is that it does not show specific protein changes but only shows changes on a mRNA level which leaves to question the complex intracellular cascades that may also be affected.

The following meta-analysis is important because it analyzes multiple studies. Thus, researchers were able to minimize some degree of error that individual studies may possess. In order to be included in this analysis, Huang, Wang, and Hu (2016) only included studies that were randomized-control trials, used probiotics as an intervention, used similar scales for evaluating depression symptoms, scales reported were mean standard deviations, and included a

control group. They evaluated the potential use of probiotics to improve depression scores in five studies, which looked at 183 cases and 182 control subjects.

While most of the individual studies did not show significant results, information from all five studies combined showed a significant reduction in depression scores in patients aged 60 and younger with probiotic supplementation, MD = -.30 (95% CI: -0.51- -0.09), p = 0.005. They included patients with existing depression and no diagnosed depression. By looking at both healthy and affected patients, it suggests that there is a possible role for probiotics in not only the treatment, but also the prevention of depression.

Rao et al. (2009) performed a study that looked at treating Chronic Fatigue Syndrome (CFS) with Lactobacillus casei. This study is somewhat different than this paper's theme of treating depression and anxiety, however, it is beneficial research because anxiety is the most reported symptom in patients with CFS. This randomized, double-blind, placebo-controlled pilot study looked at 39 participants with CFS who were randomly placed in placebo groups or treated with 24 billion colony forming units of L. casei probiotic. They were evaluated using BDI prior to and after the intervention.

In order to be included in the study, participants ranging 18-65 were screened from a pool of patient with CFS. Screened individuals that met criteria for a psychiatric disorder other than anxiety, depression, or were medically unstable were excluded. Of the 39 remaining participants, groups were randomized. Stool samples were collected prior to the initiation and analyzed for microbiome composition. After the eight-week trial, stool samples were again analyzed. Lactobacillus measurements in the placebo group participants showed a 43.8% increase and 73.7% increase in the treatment group. The increase with direct treatment would be expected, however, when the fecal total of Bifidobacteria was measured, it showed a 37.5% increase versus

a 73.7% increase in the treatment group. This is relevant because this strain of probiotic was not directly treated and showed increased growth of "healthy" bacteria through supplementation with Lactobacillus. Of additional significance, patients with CFS typically have lower levels of Bifidobacteria reported.

Participants receiving the intervention had significantly lower BDI scores at the end of the eight-week trial ($p<0.011$). While this study certainly has limitations with sample size, it is one of the only studies to look at an individual probiotic strain to treat symptoms of anxiety. It is also beneficial because of its data showing that Lactobacillus supplementation can completely displace pathogenic gut bacteria by the changes in gut microbiome constitution. This correlates with current research regarding treatment of Clostridium difficile (C. dif). Bowel function was not assessed in this study, although poor bowel function can often be a significant symptom in patients with CFS. While this study is encouraging, it should be motivation for additional, larger studies to be performed.

Kazemi, Noorbala, Azam, Eskandari and Djafarian (2019) performed a larger study involving 81 participants that assessed the effect of probiotics and prebiotic supplementation on BDI scores. While probiotics work by directly instilling bacteria within the gut, treatment with probiotics are aimed at fertilizing favorable bacteria and therefore, stimulating growth. This eight-week study was conducted as a double-blind, placebo-controlled, randomized trial and initially involved 110 patients with diagnosed depression. Eighty-one subjects finished the study and the results supported the role that probiotics play in improving symptoms of depression.

Participants were randomly assigned to receive probiotics, prebiotics, or placebo for eight weeks. The probiotics given were Lactobacillus helveticus and Bifidobacterium longus, which has been previously studied in smaller studies as having anti-inflammatory properties. BDI

scores were significantly lower in patients treated with the probiotic versus the placebo or prebiotic ($p = 0.042$). In addition to BDI scores, kynurenine/tryptophan ratios were measured and found to be significantly lower in patients treated with probiotics versus the placebo group after adjustments for serum isoleucine ($p = 0.048$). There was no significance in the prebiotic group. This is of special interest because the kynurenine tryptophan pathway has been previously implicated in the pathophysiology of depression. It is believed that the metabolites of the kynurenine tryptophan pathway cause a deficiency in serotonin, a well-known target in depression medications. This study is beneficial because it evaluates symptoms and etiology of the disease. While the study contains strong data to support the use of probiotics, an important limiting factor is that patients were not treated with the same antidepressant regimens.

The following study by Xu et al. (2018) evaluates the relationship between addiction disorders and the development of a coexisting mood disorder. While the etiology of alcohol addiction is not completely understood, it is one of the most prevalent neuropsychiatric diseases with over 3 million deaths annually. One of the key components of chronic alcoholism is the development of depression and anxiety. This is believed to be caused by the alterations in gut microbiome caused by chronic alcohol intake. Xu et al. attempted to not only prove the gut microbiome alterations caused by chronic alcohol intake, but also to treat the randomized participants with FMT from healthy donors to show the protective effect of a healthy gut against the development of mood disorders.

In order to first establish chronic alcohol usage effect on behavior, they recorded the activity of 110 mice that were in the control group or treated with increased levels of alcohol ranging from two to eight percent over a three-week period. Results of the study showed that the alcohol mice traveled less distance in the inner zone ($P = 0.0009$), spent less time in the inner

zone (P = 0.0078), had decreased mobility in the tail suspension test (TST) (P= 0.0220), and had less mobility time in the swim test (P = 0.0360). All are indicative of increased anxiety and depression-like behaviors.

After the depression and anxiety behaviors had been established, mice were randomly divided and treated with FMT from three healthy males with no history of depression. Groups were initially treated for two, which showed decreased immobility during the TST (P = 0.0026). Otherwise, no difference was observed in the other four behavioral tests. Since the results did not correlate with the expected results, the second phase of the test was repeated with mice receiving FMT for a total of five weeks. The results of this test revealed improved anxiety-like behaviors in the open field test total distance (P < 0.0001) and inner distance (P = 0.0003). Additionally, an increased TST (P < 0.001) correlated with improved depression behaviors. The results of this study showed that an increased length of FMT treatment improved symptoms in alcohol induced anxiety and depression. Interestingly, this study did not find any statistical reduction in alcohol preference. This means that while FMT may be a potential target for treatment of depression and anxiety, it did not affect the underlying cause, alcoholism.

Discussion

In patients with depression or anxiety, do gut microbiota transplants improve symptoms of depression?

Research by Bambling et al. (2017), found that twice daily dosing of probiotic capsules with Lactobacillus acidophilus, Bifidobacterium bifidum, Streptococcus thermophiles, and magnesium orotate improved depression scores in participants with SSRI resistant depression. A larger study by Kazemi et al. (2019), found an improvement in BDI depression scores after

treatment with a probiotic. The study also found that pre-treatment with a probiotic did not affect the BDI scores, which may be attributed to the replacement of pathologic bacteria in symptomatic patients in contrast to participants not exhibiting signs of depression. Of particular interest, because of large sample size, the meta-analysis performed by Huang et al. (2016), showed decreased depression scores in participants under 60 with probiotic supplementation. While the studies are certainly limited by sample size, there is significant data to suggest the need for further research into microbiome alterations as treatment for mood disorders.

In patients with depression or anxiety, is there an alteration in gut microbiota associated with the development of moods disorders?

According to the researched performed by Jianguo et al. (2019), the study analyzed gut microbiome and quantified neurotransmitters in participants with anxiety and depression. Their research found a reduction in all 12 neurotransmitters that were evaluated. Specifically, neurotransmitters that are the target of medication therapy in the current treatment of anxiety and depression. Additionally, Naseribafrouei et al. (2012), found an overrepresentation of Alistipes and Oscillibacter bacteria in participants with diagnosed depression. In order to further connect bacterial overgrowth and decreased neurotransmitters, Lou et al. (2012), found that the overgrowth of pathologic bacteria increased inflammatory markers within the brain, which in turn caused decreased neurotransmitters. The information within these studies show more than a correlation between gut bacteria and neurologic health. They also show a pathophysiologic cause between the gut and mood disorders by quantifying neurotransmitters that are the current target of treatment.

Applicability to Clinical Practice

Mood disorders, such as anxiety and depression, will be seen very frequently in all facets of health care, because it affects more than 8% of the population, often simultaneously. It is important to have a good understanding of etiology and the most up-to-date treatments. Current treatment regimens are not well targeted and are currently aimed at treating the deficiency in neurotransmitters and not treating the underlying problem. Patients will often have to experiment with multiple medications to find a regimen that is effective for them and these can become ineffective for many people over time.

My research found an underlying cause of mood disorders that links the gut microbiome, which creates another target of treatment. Increased growth of pathologic bacteria, inflammatory markers, and decreased neurotransmitters are all seen in individuals affected with mood disorders. Transplantation of their gut microbiome reproduces their symptoms in previously healthy people. My research also found lower depression scores when pathologic bacterium were replaced through transplantation with probiotics. This research is not only a compelling cause for further research into direct replacements, but also shows that probiotic supplementation may be beneficial with the current level of research.

In the future, patients may be able to have their gut microbiome analyzed and have a targeted treatment specifically designed for them. Additionally, information from these studies may be correlated with current treatment to provide patients with resistant mood disorders better treatment regimens.

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